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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB1734f-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/51043	International filing date *(day/month/year)* 17.12.2003	Priority date *(day/month/year)* 23.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D401/14		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	09.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Wörth, C Telephone No. +49 89 2399-8726

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/51043

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-38 as originally filed

Claims, Numbers

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

1. **Reference is made to the following documents:**
   D1: WO 02 062784 A
   D2: WO 97 16440 A
   D3: WO 02 32867 A
   D4: WO 97 24356 A

2. **Section V: Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**
   The present application claims compounds characterized by a **piperidine-piperazine-azepane backbone** as tachykinin antagonists useful in the treatment of emesis, anxiety depression and IBS.

2.1 Novelty

The present application differs from the content of prior art documents D1-D4 in the (optionally substituted) **azepyl moiety**. The corresponding prior art moieties are

in document D1:	pyrimidinyl, pyridinyl and pyrizanyl (see definition of R^1, page 1, lines 17-25)
in document D2:	fused imidazolyl (see page 2, formula (a-4), when Y^2 is a bond)
in document D3:	hydrogen, alkyl or $C(O)R_6$ (see page 2, definition of R^5)
in document D4:	a tricyclic moiety according to the definition of L

The requirements of novelty are fulfilled.

2.2 Inventive step

Document D1 is considered as **closest prior art**. This document discloses on page 3 and in claim 9 piperidine-4yl-piperazine-1yl-derivatives of formula IC as antagonists of NK-1 (see page 6, lines 3-9).

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those disclosed in document D1.

The **solution** to this problem consists in the provision of compounds of present

claim 1 characterized by a **piperidine-piperazine-azepane backbone.**

In view of the pharmacological data provided on page 32 and 33 of the description, the problem posed is considered as **solved.**

Document D1 discloses compounds of formula IC characterized by a piperidine-piperazine-backbone, whereby the piperazine moiety is optionally substituted at position 4 by several N-containing 6-membered heterocycles such as pyridine, pyrimidine and pyrazine thereby indicating a certain variability of the corresponding terminal group without impact on the desired activity.

This technical teaching is confirmed by documents D2-D4 defining the corresponding moiety (see definitions of L in D2 and D4 and definition of R^5 in D3) as a range from hydrogen up to tricyclic derivatives without impact on the desired activity.

However, the compounds of the present application are equally or more potent NK1-antagonists than the compounds according to D1 (see D1, page 23, lines 19-21). Furthermore, the introduction of a substituted azepane moiety introduces NK-3 antagonistic activity giving the compounds of the present application a combined NK1/NK3-antagonism activity being beneficial for the treatment of schizophrenia, pain and inflammation. This unexpected effect indicates an inventive step.

The requirements of inventive step are fulfilled.

2.3 Further remarks

a) Claim 9 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

b) Claims 11-18 should be renumbered since claim 10 is missing.

c) The term "central penetrating medicine" used in claim 11 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim/s unclear, Article 6 PCT.